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Staying Awake in Severe ARDS – A Perspective on Immunocompromised Patients

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To the Editor,

We read with great interest the recent report in the *Journal* of Dumas and colleagues summarizing extensive data on ventilation strategies in immunocompromised patients with acute respiratory failure (ARF) (1). The authors concluded that delayed intubation might be independently associated with increased mortality in immunocompromised patients.

Pickkers and van Haren challenged this conclusion in their thoughtful editorial by emphasizing several important limitations of the study, including incomplete available data from all included studies and the overall small number of randomized studies conferring the risk of several confounding issues (2). The most important limitation is based on the fact that all non-invasively ventilated patients included in this meta-analysis were eventually intubated, not allowing any robust statements about inferiority of non-invasive techniques per se.

We agree with our colleagues that this introduces a strong selection bias, as patients who will eventually fail non-invasive ventilation (NIV) might differ in many characteristics from those that might be successfully bridged with a NIV strategy. Bearing in mind the exceedingly high mortality of immunocompromised patients requiring invasive mechanical ventilation (1), we believe it would be premature to advise towards a general rule of early intubation in all of these patients.

Ventilator induced lung injury, ventilator acquired pneumonia and ventilator induced diaphragm dysfunction are well-known side effects of invasive ventilation and may contribute to and aggravate the complex pathophysiology of multi-organ failure and death in ARF (3). The use of extracorporeal membrane oxygenation (ECMO) in non-intubated patients who are awake and spontaneously breathing (termed awake ECMO) might theoretically avoid side effects and complications associated with sedation, intubation, and

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invasive mechanical ventilation (4). We recently described our single-center experience with a primary awake ECMO strategy in 18 non-intubated immunocompromised patients with severe acute respiratory distress syndrome (ARDS) (median P_aO_2/F_iO_2 72 (65-82)) who presented without secondary organ dysfunction (5). During their ICU stay, 11 patients (61%) required secondary intubation. Of note, the most common reason for secondary intubation was severe agitation. In-hospital mortality was 73% in patients who required secondary intubation versus 14% in patients who did not require intubation while on ECMO support (Hazard Ratio: 0.133 (0.058 – 0.789; p=0.023).

Although limited by the small sample size and the uncontrolled nature of the study, we believe that these data demonstrate as a *proof of principle* that in selected immunocompromised patients with ARDS, an awake ECMO strategy may be used to avoid intubation and mechanical ventilation. Of course, further data is needed, but the high mortality of immunocompromised patients who require mechanical ventilation warrants the exploration of alternative strategies.

A patient individualized approach considering all available options and continuously weighing the benefits of avoiding the well-known side effects of invasive ventilation while not ignoring the risks of patient self inflicted lung injury (P-SILI) (6) provoked by delaying intubation for too long, clearly will be critical on our path towards improving the care of immunocompromised patients with ARF.

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